

EFFICACY AND TOLERABILITY OF RISPERIDONE IN THE TREATMENT OF DEPRESSIVE DISORDERS

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Abstract

The aim of this paper was to assess the efficacy and the tolerability of the therapy with risperidone in the case of depressive disorders. 84 adult subjects aged 18-65 years were randomized into two groups: 42 patients into lot A treated with risperidone (1-2mg/day) and 42 subjects lot B, *placebo*.

Symptoms were measured using the 17-item Hamilton Rating Scale for Depression (HRSD-17). Other outcomes were the response to therapy, and the adverse events. Mean HRSD-17 scores improved more in the risperidone group than in the *placebo* group. Headache (19.04% of risperidone group vs. 26.19% of *placebo* group), somnolence (16.67% vs. 4.76%), dry mouth (9.52% vs. 7.14%), nausea (4.76% vs. 11.91%) and weight gain (14.28% vs. 7.14%) were the most frequently reported adverse events. Risperidone produced significant reduction in depression symptoms having a good tolerability.

Rezumat

Scopul acestei lucrări a fost evaluarea eficacității și tolerabilității terapiei cu risperidonă la pacienții cu maladie depresivă. 84 de subiecți cu vârsta între 18-65 ani au fost randomizați în două grupuri: 42 pacienți în lotul A tratați cu risperidonă (1-2 mg /zi) și 42 de subiecți în lotul B, *placebo*.

Simptomele au fost evaluate cu Scala de Depresie Hamilton (*Hamilton Rating Scale for Depression*, HRSD-17). S-a înregistrat de asemenea și răspunsul la terapie precum și incidența reacțiilor adverse. Media scorurilor HRSD-17 s-a îmbunătățit mai mult în grupul tratat cu risperidonă decât în cel *placebo*. Cefaleea (19.04% pentru grupul tratat cu risperidonă vs. 26.19% pentru grupul *placebo*), somnolența (16,67% vs. 4,76%), uscăciunea gurii (9,52% vs. 7,14%), grețurile (4,76% vs. 11,91%) și creșterea ponderală (14,28% vs. 7,14%) au fost cele mai raportate efecte adverse. Risperidona a produs o reducere semnificativă a simptomatologiei depresive, fiind însoțită de o bună tolerabilitate.

Keywords: Risperidone, depressive disorders

Introduction

Major depressive disorder represents a chronic and recurrent illness, affecting more than 320 million people worldwide [1]. It is considered a very important etiology of disability, being associated with increased mortality and morbidity, premature cardiovascular-related death, and lost of productivity [2, 3, 4]. A major factor contributing to this health burden is the high rate of relapse and recurrence. Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors are considered first-line treatments for depression. Initial antidepressant therapy significantly reduces symptoms of depression in many patients, only 50–60% of patients with major depressive disorder respond to treatment [5]. Between 30 and 40% of the persons who suffer from major depressive disorder never achieve symptoms resolution with standard antidepressant therapy. This has stimulated the research for more effective treatment alternatives [6]. Risperidone's unique receptor binding profile distinguished by potent antagonism of the serotonin 5-HT_{2A}, dopamine D₂, and alpha-adrenergic_{2C} receptors—has been considered to be relevant for the treatment of affective disorders [7]. A possible hypothesis is that low-doses of risperidone would reduce symptoms of major depressive disorder, enhance clinical response and remission rates, and diminish disability compared with continued antidepressant monotherapy. Existing data suggest that persons with a confirmed suboptimal response to previous treatment may respond to risperidone augmentation within 4 to 6 weeks [8]. According to these ideas we performed a prospective randomized study to assess the clinical efficacy of risperidone, to evaluate tolerability in patients with major depressive disorder.

Materials and methods

This study was a randomized prospective one, performed from June 2006 to January 2007 in the Psychiatry Department of the Municipal Hospital of Timis county. It was approved by the institutional ethics committee and written informed consent was obtained from each subject. This study included three phases: 1) 4–6 weeks of antidepressant monotherapy to confirm the non-response to a standard therapy with SSRI; 2) 4–6 weeks of risperidone treatment to evaluate the augmentation effects relative to SSRI monotherapy and to identify patients with symptom resolution; and 3) a 24-weeks double-blind discontinuation phase to assess the effect of augmentation with risperidone *versus placebo* in the prevention of relapse.

A number of 84 subjects (43 males and 41 females) were enrolled,

aged 18–65 years, meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[9] diagnostic criteria for major depressive disorder, single or recurrent episode, and with a Hamilton Rating Scale for Depression (HRSD-17) total score ≥ 20 . The Hamilton Rating Scale for Depression is a 21-question multiple choice questionnaire that clinicians use to rate the severity of a patient's major depression. The first 17 questions contribute to the total score (HRSD-17), the rest being recorded to give further information about the depression [10]. Subjects were required to have a history of resistance to standard antidepressant therapy, defined as failure to respond to at least one but not more than three adequate antidepressant stage during the current episode. Exclusion criteria were: all other DSM-IV axis I diagnoses, including dementia and bipolar disorder (type I or II) as well as a lifetime diagnosis of DSM IV borderline personality disorder, pregnancy; serious suicidal risk or serious medical or neurological illness; active substance or alcohol use disorders; current treatment with a tricyclic antidepressant, monoamine oxidase inhibitor, mood stabilizer, antiepileptic, or a central acting agent for attention deficit disorder/attention deficit hyperactivity disorder or narcolepsy. All subjects received a complete medical history, physical examination, laboratory evaluation, including chemistry panel, liver panel, complete blood count, urine analysis, and electrocardiography.

The subjects eligible for randomization were assigned to receive risperidone or *placebo*. Tablets were identical in appearance. The dosing was 0.25 mg/day for the first 3 days, 0.5 mg/day on days 4 to 15, and 1.0 mg/day on days 16 to 28. On day 29, patients with insufficient treatment response in the opinion of the investigator could continue augmentation of the current dose, by increasing it to 2 mg/day.

The efficacy assessments included various scales designed for the measurement of symptoms of depression. The Montgomery–Asberg Depression Rating Scale (MADRS) [11], a 10-items scale that assesses a range of depressive symptoms, was the primary outcome measure used to assess the depression severity. The HRSD-17 evaluates depressed mood as well as the neurovegetative and cognitive symptoms of depression. The HRSD-17 was used as a screening tool to determine subject eligibility for the three phases of the study and as one relapse criterion. A change in the HRSD-17 total score from baseline to the study end was the primary efficacy measure. Response ($\geq 50\%$ reduction in HRSD-17 total score from baseline) and remission (HRSD-17 total score ≤ 7) were assessed at each time point. The Clinical Global Impression –Severity scale (CGI-S scale) ratings were the risperidone augmentation phase (baseline, day 4, weeks 1,

2, 4, and 6) [12]. Safety assessments included reports of spontaneous adverse events collected at every visit. Vital signs, electrocardiograms, and laboratory test results were obtained. The Abnormal Involuntary Movement Scale (AIMS; for dyskinesia and dystonia) [12], the Simpson–Angus Rating Scale (SAS; for parkinsonism) [14], and the Barnes Akathisia Scale (BAS) [13] were completed at regular intervals to measure movement disorders. All adverse events were recorded, and the investigator assessed each event for severity and relationship to the studied drug. Statistical analysis was performed with EPI Info 6 software.

Results and discussion

Socio-demographic characteristics of the 84 patients selected and divided into 2 groups: a) lot A 42 subjects treated with risperidone b) lot B 42 subjects that received *placebo*, are presented in Table I.

Table I
Comparative socio-demographic characteristics of patients

Characteristic*	Lot A Risperidone (n=42)	Lot B Placebo (n=42)
Sex, n [%]		
Female	31 (73.81)	32 (76.19)
Male	11 (26.19)	10 (23.81)
Age [Mean±SD]	45±4.82	46±3.96
Urban area, n [%]	39 (92.85)	38 (90.47)
Education, n [%]		
Primary school	14 (33.34)	12 (28.56)
High school	21 (50.00)	24 (57.15)
College graduate	7 (16.64)	6 (14.29)
Employment status [%]		
Full-time	20 (47.62)	21 (50.00)
Retired	13 (30.96)	12 (28.57)
Unemployed	9 (21.42)	9 (21.43.)

*CI -Confidence interval
CI 95%; $p < 0.05$

Baseline demographic characteristics were similar between groups at the start of the study. Patients reported an important history of depression (mean time since diagnosis, 14.92 ± 1.45 years). At the beginning of the study, the groups were evaluated for mean ($\pm$ SD) HRSD-17 scores

(24.2 ± 0.50 among risperidone group vs. 24.4 ± 0.51 among *placebo* lot; $p < 0.05$).

The comparative evolution of the severity of depression symptoms measured with HRSD-17 score is presented in Figure 1.

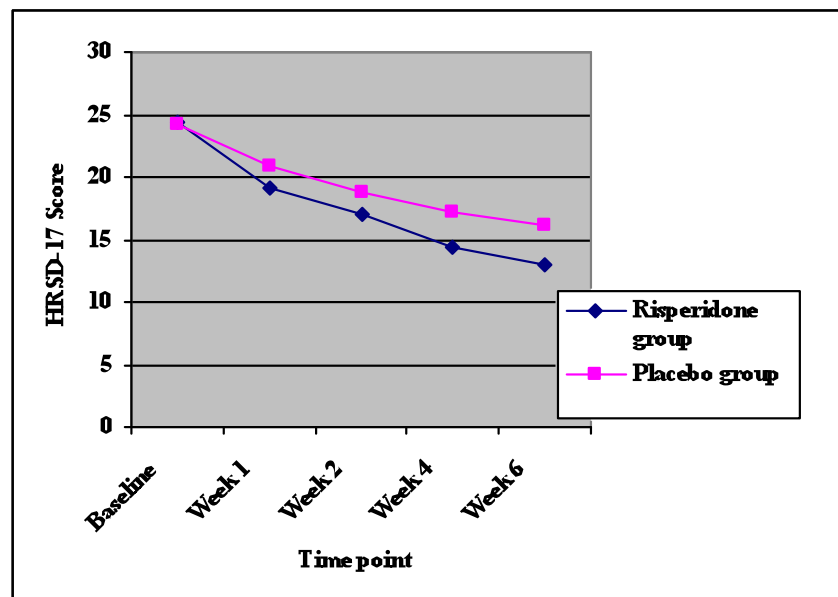


Figure 1

Comparative evaluation of the severity of depression with HRSD-17 Score

According to the model, repeated measures analysis, the severity of depression symptoms, as measured by HRSD-17 score, improved more in the risperidone group than in the placebo group both in the 6th week.

The evaluation using the Clinical Global Impression–Severity of illness scale (CGI- S) is presented in the following table (Table II).

Table II

Clinical Global Impression–Severity of illness scale (CGI- S)

Parameter*	Risperidone group Score [mean value±SD]	Placebo group Score [mean value±SD]
CGI-S		
Baseline	4.5±0.03	4.5±0.06
Week 6	2.5±0.02	3.5±0.08

*CI 95%; $p < 0.05$

The CGI-S score was significantly improved in the 6th week in the risperidone group than in the placebo lot.

Table III
Comparative incidence of adverse events during the study

Parameter*	Risperidone group (n=42)	Placebo group (n=42)
Any treatment emergent adverse event n [%]	20 (47.62)	22 (52.38)
Gastrointestinal disorders		
Constipation n[%]	2 (4.76)	1 (2.38)
Diarrhea n[%]	1 (2.38)	3 (7.14)
Dry mouth n[%]	4 (9.52)	3 (7.14)
Dyspepsia n[%]	2 (4.76)	4 (9.52)
Nausea n[%]	2 (4.76)	5 (11.91)
General disorders		
Fatigue n[%]	5 (11.91)	0
Peripheral edema n[%]	4 (9.52)	1 (2.38)
Weight gain n[%]	6 (14.28)	3 (7.14)
Musculoskeletal disorders		
Arthralgia n[%]	2 (4.76)	3 (7.14)
Back pain n[%]	0	3 (7.14)
Nervous system disorders		
Disturbance in attention n[%]	3 (7.14)	0
Dizziness n[%]	3 (7.14)	5 (11.91)
Headache n[%]	8 (19.04)	11 (26.19)
Somnolence n[%]	7 (16.67)	2 (4.76)
Insomnia n[%]	4 (9.52)	4 (9.52)
Hypertension n[%]	0	3 (7.14)

*CI 95%; $p < 0.05$

Adverse events associated with the therapeutical protocol were similar in nature and occurred at a similar frequency in both groups. In our case, motor effects potentially associated with antipsychotic therapy, particularly at the higher doses used to treat psychotic disorders, were infrequent.

The primary finding of this study suggests that risperidone is associated with symptom resolution for a significant number of patients. The rapid reduction in HRSD-scores is similar to that seen in previous smaller studies of atypical antipsychotic augmentation of SSRI-resistant depression. [15, 16]

Time to onset of effect is an important problem in the treatment of depression. In our study, risperidone therapy offered statistically significant benefit on multiple measures within 1 week, and the magnitude of benefit appeared to increase steadily throughout the study.

The risk-to-benefit ratio is an important issue; we identified no unexpected adverse events and those that were reported were similar, generally mild, and of short duration in both groups. More placebo patients

than risperidone ones reported an adverse event (52.38% vs. 47.62%).

The doses of risperidone (0.25 to 2.0 mg/day) that we tested are notable, because the ratio of relative affinity of risperidone for serotonin to dopamine receptors is higher than that observed at the doses generally used for psychotic disorders (for example, up to 6 mg/day). Therefore, effects in depression may not be similar in a different dosage range. In addition, different atypical antipsychotics have different patterns of neurotransmitter receptor activity; caution is warranted in generalizing findings to differently acting medications [17, 18, 19, 20, 21].

A previous controlled trial evaluated relapse prevention among patients who achieved full remission with risperidone therapy. In literature, there are authors who treated the patients with less than 50% symptom improvement after 4 weeks of prospective SSRI treatment with open-label adjunctive risperidone and found that 63% achieved symptom remission (HRSD-17 score ≤ 7) after 6 weeks [8].

Our findings suggest that risperidone augmentation is well tolerated and has beneficial effects early in the course of treatment among patients who do not respond to the initial protocol. Additional research is needed to define the dose, duration, and treatment strategy for risperidone augmentation in daily practice, and ultimately to provide new and better treatments for the many patients with major depressive disorder whose needs continue to be underserved.

Conclusions

The treatment of depression represents a common challenge that clinicians and patients must face.

The results of the present study demonstrate that risperidone is a reasonable and safe strategy that is helpful for some patients with depressive disorder.

We found that risperidone was associated with improvements in clinical depressive symptoms, reduced disability, and increased response and remission rates.

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